Clinical and Experimental Human Sleep-Wake Pharmacogenetics

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CLINICAL AND EXPERIMENTAL HUMAN SLEEP-WAKE PHARMACOGENETICS

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Abstract

Sleep and wakefulness are highly complex processes that are elegantly orchestrated by fine-tuned neurochemical changes among neuronal and non-neuronal ensembles, nuclei and networks of the brain. Important neurotransmitters and neuromodulators regulating the circadian and homeostatic facets of sleep-wake physiology include melatonin, γ-amino-butyric acid, hypocretin, histamine, norepinephrine, serotonin, dopamine, and adenosine. Dysregulation of these neurochemical systems may cause sleep-wake disorders, which are commonly classified into

insomnia disorder, parasomnias, circadian rhythm sleep-wake disorders, central disorders of hypersomnolence, sleep-related movement disorders, and sleep-related breathing disorders. Sleep-wake disorders can have far reaching consequences on physical, mental and social well-being and health and, thus, need be treated with effective and rational therapies. Apart from behavioral (e.g., cognitive behavioral therapy for insomnia), physiological (e.g., chronotherapy with bright light), and mechanical (e.g., continuous positive airway pressure treatment of obstructive sleep apnea) interventions, pharmacological treatments often are the first-line clinical option to improve disturbed sleep and wake states. Nevertheless, not all patients respond to pharmacotherapy in uniform and beneficial fashion. The improved understanding of the neurochemical mechanisms regulating sleep and wakefulness and the mode of action of sleep-wake therapeutics has provided a conceptual framework, to search for functional genetic variants modifying individual drug response phenotypes. This article will summarize the currently known genetic polymorphisms that modulate drug sensitivity and exposure to partly determine individual responses to sleep-wake pharmacotherapy. In addition, a pharmacogenetic strategy will be outlined how based upon classical and opto-/chemogenetic strategies in animals, as well as human genetic associations, circuit mechanisms regulating sleep-wake functions in humans can be identified. As such, experimental human sleep-wake pharmacogenetics forms a bridge spanning basic research and clinical medicine and constitutes an essential step for the search and development of novel sleep-wake targets and therapeutics.

Keywords

Polymorphism; pharmacokinetics; pharmacodynamics; circadian; melatonin; GABA; orexin; H_3 receptor; adenosine; dopamine

Introduction

Wakefulness and sleep are complex behavioral processes, which are elegantly orchestrated by fine-tuned interactions of neurotransmitter and neuromodulator systems within defined wake-sleep circuits of the brain. Over the past 100 years, clinical observations in patients suffering from sleep-wake disorders and basic research spanning from *in vitro* preparations and animal models to healthy human volunteers, have led to a widely accepted neurobiological model underlying the physiological alterations between wakefulness and distinct sleep states (for review, see (Holst et al., 2016)). More specifically, wakefulness and cortical arousal are thought to be governed primarily by concerted activity in upper brain stem and hypothalamic nuclei, which produce acetylcholine (Ach), norepinephrine (NE), serotonin (5-HT; 5-hydroxy-tryptamine), dopamine (DA), histamine (His) and hypocretin (Hcrt; *aka* orexin) as their neurotransmitters. These nuclei activate thalamus, cortex and spinal cord, and inhibit the sleep-promoting ventro-lateral preoptic (VLPO) area of the hypothalamus.

The regulation of sleep differs substantially between the non-rapid-eye-movement (NREM) and rapid-eye-movement (REM) sleep states. NREM sleep is supposed to be promoted by GABA- (γ-amino-butyric acid) and galanin-containing neurons originating in VLPO and median preoptic nuclei of the hypothalamus. These nuclei inhibit the wake-promoting arousal systems described above. On the other hand, REM sleep exhibits both, 'wake-like' and 'sleep-like' characteristics. 'Wake-on'-'REM-on' basal forebrain (BF) and brain stem nuclei containing Ach and glutamate activate the BF and cortex, induce muscle atonia, and promote rapid eye movements. In addition, hypothalamic neurons containing melanin-concentrating hormone suppress the activity of 'Wake-on'-'REM-off' cell groups, which primarily include the upper brainstem monoaminergic nuclei.

Powerful new tools to interrogate sleep-wake regulating circuits, including sophisticated optogenetic and chemogenetic experiments, have revealed new molecular and cellular markers, as well as novel network mechanisms and pathways in sleep-wake regulation. These recent insights

may necessitate an adaptation of the basic sleep-wake neurochemistry described above. They have been discussed in comprehensive reviews and other chapters of this book (Adamantidis and Luthi, 2018 ; Saper and Fuller, 2017; Tyree and de Lecea, 2017; Eban-Rothschild et al., 2018; Luppi and Fort, 2018; Varin and Bonnavion, 2018), and are not the focus of this chapter. In this article, firstly, genetic aspects of the current pharmacotherapy of sleep-wake disorders will be reviewed. Secondly, an experimental pharmacogenetic strategy to identify circuit mechanisms underlying sleep-wake regulation in humans will be outlined.

Current Sleep-wake Pharmacotherapy

Based on the 'standard model' of sleep-wake circuitry, subtle changes in important neurotransmitters and neuromodulators (including NE, 5-HT, DA, His, Hcrt, melatonin, glutamate, Ach, GABA, and adenosine) regulate not only the transitions among the behavioral states wakefulness, REM sleep and NREM sleep, but also their maintenance (Holst and Landolt, 2018). Dysregulation of these fine-tuned neurochemical systems can lead to sleep-wake disturbances. According to the 3rd edition of the International Classification of Sleep Disorders, sleep-wake disturbances are subdivided into the following major diagnostic sections: insomnia disorder, circadian rhythm sleep-wake disorders, sleep-related breathing disorders, sleep-related movement disorders, central disorders of hypersomnolence, parasomnias, and other sleep disorders (2014). Some of these pathologies are typically treated with pharmacological agents as summarized and reviewed in Part III of this book (insomnia and circadian rhythm sleep-wake disorder: (Spiegelhalder et al.); hypersomnias and sleep-related movement disorders: (Baumann, 2018)). All drugs presently used to treat the symptoms of sleep-wake disorders interfere with the neurochemical and neuromodulatory systems mentioned above (Idzikowski, 2014; Holst et al., 2016). Thus, although the 'standard model' of the neuroanatomical and neurochemical regulation of wakefulness and sleep will have to be adapted, it provides a useful conceptual framework for understanding the effects of

the medications currently used to improve sleep and wake states (**Figure 1**).

Insomnia Disorder

Drug treatment is often used for short-term alleviation of insomnia symptoms. When combined with behavioral therapy, pharmacological treatments show durable improvements in sleep patterns (Riemann and Perlis, 2009). Conceptually, disturbed sleep can be pharmacologically improved by compounds that either promote sleep or dampen the wake-promoting systems.

Agonistic modulators of $GABA_A$ receptors such as benzodiazepines and Z-drugs (e.g., zolpidem) enhance the inhibitory inputs of GABA-containing neurons that inhibit the ascending arousal pathways (Finelli et al., 2000). These compounds act as positive allosteric modulators and, at higher doses, as agonists of $GABA_A$ receptors. They are often prescribed for the short-term pharmacological treatment of insomnia disorder and show demonstrated efficacy in shortening sleep latency and improving sleep maintenance (Dresler et al., 2014). Absolute effect sizes, however, may be rather small when compared to placebo (Wilt et al., 2016). In standard clinical practice of pharmacologically treating insomnia, benzodiazepines and Z-drugs have largely replaced the previously used barbiturates.

The dual orexin receptor antagonist (DORA), suvorexant, was recently approved by the US Food and Drug Administration (FDA) for treating insomnia disorder in adults (Wilt et al., 2016). Suvorexant acts by antagonizing wake-promoting Hcrt neurons located in the lateral hypothalamus. Some authors claim that surovexant elicits more physiological sleep than benzodiazepines (Patel et al., 2015). Nevertheless, the compound seems to mainly prolong REM sleep and stage 2 sleep, with marginal effect on deep slow wave sleep (Hoyer and Jacobson, 2013).

Drugs antagonizing key monoaminergic nuclei of the ascending arousal pathways commonly cause sleepiness. One example of such a mode of action is the blockade of H_1 receptors to antagonize wake promotion by His. ‘Antihistamines’ such as diphenhydramine and doxylamine have

long been available over-the-counter and are sometimes used to treat insomnia. Similarly, tricyclic and heterocyclic antidepressants and antipsychotics are often associated with sleepiness, probably related to their antihistamine and possibly other "off-target" receptor interactions (such as anticholinergic effects). Low doses of doxepin are FDA-approved to treat insomnia by promoting sleep onset (Goforth, 2009). Other sedating antidepressant and antipsychotic medications are more and more commonly prescribed "off-label" as sleeping pills (Proctor and Bianchi, 2012; Krystal et al., 2013). Apart from H_1 and muscarinic ACh receptors, some of these agents (e.g., mirtazapine) have high affinity for 5-HT_{2A} and adrenergic α_1 receptors. Blockade of these receptors facilitates sleep. Conversely, these compounds often also inhibit 5-HT and NE re-uptake transporters and antagonize 5-HT_{2C} and α_2 receptors and thus promote wakefulness, which detracts from the sleep-promoting effects of blocking the H_1 receptors (Krystal et al., 2013).

Parasomnias

The most commonly used drugs for NREM sleep parasomnias are intermediate- and long-acting benzodiazepines and antidepressants (Castelnovo et al., 2018). The pharmacologic treatment of REM sleep behavior disorder presently relies primarily on the benzodiazepine, clonazepam, whereas melatonin and melatonin receptor agonists may be equally efficacious with less unwanted effects (McGrane et al., 2015; Castelnovo et al., 2018).

Circadian Rhythm Sleep-Wake Disorders

The circadian resetting effects of melatonin are well documented. Interference with both melatonin MT_1 and MT_2 receptor subtypes, contributes to the distinct phase-response profile of melatonin (Burgess and Emens, 2018). Melatonin alone or in combination, as well as different melatonin analogues, are available either without prescription or as regulatory-approved drugs. There is increasing interest in the potential of melatonin-based therapies in the treatment of

disturbed sleep (Alston et al., 2018). These therapies offer potential to treat sleep and mood disorders, especially when circadian rhythm disturbances are also present. Such disorders include insomnia induced by shifted sleep-wake cycles in healthy individuals, insomnia in older adults, delayed sleep-wake phase disorder, non-24-hour sleep-wake disorder (N24HSWD), seasonal affective disorder, and major depressive disorder (Alston et al., 2018; Burgess and Emens, 2018). Prolonged-release melatonin (Circadin®) has been approved for chronic insomnia in patients older than 55 years. In combination with antihistamines, GABA-ergic hypnotics, herbal extracts, or bright light therapy, prolonged-release melatonin may improve hypnotic efficacy (Saxvig et al., 2014; Rivara et al., 2015). Apart from N24HSWD, the $MT_{1/2}$ receptor agonist, tasimelteon, may also be useful in certain patients with insomnia, advanced-sleep-phase-syndrome and delayed-sleep-phase-syndrome (Lankford, 2011). Ramelteon received FDA-approval for treatment of insomnia in older adults, and the $MT_{1/2}$ agonist/5-HT_{2C} receptor antagonist, agomelatine, has EMA- and TGA (Therapeutic Goods Administration, Australia)-approval for major depressive disorder. Agomelatine phase shifts the circadian system and improves sleep in depressed patients, although its usefulness for primary sleep disorders is debated (De Berardis et al., 2015).

Central Disorders of Hypersomnolence

Central disorders of hypersomnolence are characterized by excessive daytime sleepiness (EDS), often despite apparently normal quality, duration and timing of nocturnal sleep. These disorders include narcolepsy type-1 (characterized by deficient Hcrt in cerebrospinal fluid), narcolepsy type-2 and idiopathic hypersomnia. Their pharmacological treatment focuses on the management of EDS, with additional treatment of cataplexy, which is typically present in patients with narcolepsy type-1 (Baumann, 2018).

Modafinil and its (R)-enantiomer, armodafinil, are FDA-approved first-line treatments of EDS in narcolepsy (Mignot, 2012; Abad and Guilleminault, 2017). While the mode of action of

(ar)modafinil is complex and may involve NE, 5-HT, His, Hcrt, glutamate, and GABA, it increases DA-ergic neurotransmission and blocks the DA re-uptake transporter (DAT) (Wisor et al., 2001; Volkow et al., 2009; Wisor, 2018).

Amphetamine and its derivatives are treatments of second-choice against EDS in narcolepsy (Abad and Guilleminault, 2017). These compounds actively promote the presynaptic release of DA and dampen DAT function (Mignot, 2012). They cause autonomic arousal and psychomotor agitation and have strong addictive properties. Stimulants such as methylphenidate and mazindol are specific DAT inhibitors. Methylphenidate is FDA-approved for narcolepsy. Preliminary evidence also suggests therapeutic efficacy for mazindol (Nittur et al., 2013).

Certain antidepressants such as bupropion, venlafaxine and clomipramine that block the re-uptake transporters for DA (DAT), NE (NET) and/or 5-HT (SERT) are typically used against cataplexy in narcolepsy type-1 (Mignot, 2012). Tricyclic antidepressants strongly reduce REM sleep and cataplectic attacks without affecting EDS (Houghton et al., 2004). They have undesired anticholinergic and antihistaminic properties and prolonged use can cause tolerance. Dual NET-SERT inhibitors or selective NE and 5-HT re-uptake inhibitors (SSRIs) may provide alternative options to treat cataplexy (Houghton et al., 2004). Finally, monoamine oxidase (MAO) inhibitors such as selegiline are used 'off-label' against cataplexy and EDS (Thorpy and Dauvilliers, 2015).

The adenosine A_1 and A_{2A} receptor antagonist, caffeine, is the most widely used stimulant worldwide. Caffeine can improve vigilance in susceptible, sleep deprived individuals (Gottselig et al., 2006; Rétey et al., 2007), yet probably has insufficient potency in patients with clinical EDS (Banerjee et al., 2004). Sleepy people may use caffeine excessively to improve alertness (Urry et al., 2017), and a positive correlation between disease severity and habitual caffeine use was observed in patients with narcolepsy-cataplexy (Mitler et al., 1998). Intake of 200-300 mg per day, which is typical in Western societies, is generally well tolerated and does not posit a known health risk (Loftfield et al., 2018).

The safe improvement of wakefulness in hypersomnolent patients has so far proved difficult, despite the fact that the above-mentioned compounds are potent. Based on the rationale that sleep and wakefulness form a functional continuum and that improved sleep also improves the quality of wakefulness, γ-hydroxy-butyrate (GHB or the sodium salt of γ-hydroxy-butyric acid, sodium oxybate), is currently the first-line, FDA-approved agent for cataplexy and EDS in patients with narcolepsy (Thorpy and Dauvilliers, 2015; Abad and Guilleminault, 2017). This rapid sedative may also alleviate sleep disruption in narcolepsy. The exact mode of action of GHB is unknown. GHB is an endogenous short-chain fatty acid that exhibits high affinity for GHB receptors (K_D ≈ 30-580 nM) and low affinity for $GABA_B$ receptors (K_D ≈ 2.6-16 µM) (Mamelak, 2009). The stabilization of sleep continuity by supra-physiological doses of GHB may be predominantly mediated by agonistic stimulation of $GABA_B$ receptors. Thus, the $GABA_B$ receptor agonist, baclofen, may also be useful in treating patients with narcolepsy (Huang and Guilleminault, 2009; Black et al., 2014).

Histamine H_3 receptor inverse agonists such as pitolisant provide a promising new class of wake-promoting medications with possible pro-cognitive properties (Stocking and Letavic, 2008). The H_3 receptor is an inhibitory auto-receptor on pre-synaptic neurons, which attenuates the release of His and other excitatory neurotransmitters when activated (Lin et al., 2011).

It has been postulated that Hcrt neurons continuously integrate information from multiple processes, to modulate the propensity to stay awake or to fall asleep (Eban-Rothschild et al., 2018). The firing of Hcrt neurons in the lateral/posterior hypothalamus promotes wakefulness. Intra-nasal delivery of Hcrt peptide may reduce wake-REM sleep transitions and slightly improve attention after sleep in patients with narcolepsy-cataplexy (Weinhold et al., 2014).

Sleep-Related Movement Disorders

The pharmacologic treatment of restless legs syndrome (RLS) and periodic limb movement disorder during sleep traditionally relies on the dopamine D_2 receptor antagonists pramipexole,

ropinirole and rotigotine (Baumann, 2018). These dopaminergic agents, and in particular L-dopa, carry the risk of augmentation, i.e., aggravated RLS symptoms with continued medication use (Trenkwalder and Paulus, 2010). Iron supplementation in case of iron deficiency, benzodiazepines, and opiates may also be effective and are often used as secondary treatments (Winkelmann et al., 2018). Prolonged-release oxycodone-naloxone, a combined opioid analgesic and opioid receptor antagonist, has recently provided an additional option for refractory RLS (Trenkwalder et al., 2013).

Because of the frequently observed augmentation with dopaminergic agents, an international task force recently recommended α2β receptor ligands of voltage-gated calcium channels, such as gabapentin and pregabalin, as first-line option to treat restless legs (Garcia-Borreguero et al., 2016). Gabapentin and pregabalin are structurally related to GABA, increase GABA concentration the human brain (Cai et al., 2012), and inhibit calcium currents. The derivative gabapentin-enacarbil was recently approved by FDA for RLS. In contrast to the dopaminergic drugs, gabapentin-enacarbil does not lead to augmentation.

Based on the hypothesis that brain iron deficiency in RLS is associated with a hypo-adenosinergic state, a preliminary study recently suggested that the non-selective ENT1/ENT2 (equilibrative nucleoside transporter) inhibitor, dipyridamole, has significant therapeutic effects on sensory and motor symptoms, as well as sleep (Garcia-Borreguero et al., 2018).

Sleep-Related Breathing Disorders

Sleep-related breathing disorders include upper airway obstructions (obstructive sleep apnea [OSA]) and ceased or decreased ventilatory effort (central sleep apnea) during sleep. While OSA is most commonly treated with continuous positive airway pressure (CPAP) therapy, the therapeutic success of CPAP and other available therapies is often hampered by limited compliance or efficacy (Hedner and Zou, 2018). These and other reasons warrant the scientific search for pharmacological remedies of OSA. Nevertheless, currently no pharmacologic alternatives to CPAP

are available. Promising research has recently characterized different phenotypes of OSA, which may provide novel strategies and targets for drug development (Hedner and Zou, 2018).

Variable Drug Response Genetics

Gene polymorphisms modulating drug sensitivity and exposure can determine individual responses

It has long been recognized that not all patients respond to pharmacotherapy in a uniform and beneficial fashion. How a therapeutic compound affects the organism and its physiology (pharmacodynamics) and how the organism acts on such a compound (pharmacokinetics) are highly individual processes, which are, in part, genetically determined. Pharmacogenetic approaches aim at elucidating genetically determined inter-individual differences in drug responses, with the goal to discriminate responders from non-responders and to minimize toxicity and adverse drug reactions. Such studies have shown that single nucleotide polymorphisms (SNPs), variable-number-tandem-repeat (VNTR) polymorphisms, copy number variations, and insertions/deletions in genes regulating the pharmacodynamics (e.g., receptors, ion channels, enzymes, immune molecules) of medications and/or their pharmacokinetics (e.g., metabolizing enzymes, transporters, plasma protein binding) contribute to wanted and adverse actions of pharmacotherapeutic agents (Evans and Relling, 1999; Sadee and Dai, 2005; Roden et al., 2011; Holst et al., 2016).

Genes modulating the pharmacodynamic response to a pharmacological treatment may code for the direct targets of drugs (e.g., receptors) or for proteins that synthesize, clear or degrade the endogenous ligands of these targets (e.g., neurotransmitters). Functional genetic variation in these genes, thus, possibly affects drug sensitivity.

The field of pharmacogenetics has historically focused on genetically determined differences in the activity of drug-metabolizing enzymes. Functional variants of genes encoding such enzymes can modulate exposure to therapeutic agents and, thus, their efficacy and toxicity. For example, more than 80 % of all clinically used drugs are metabolized by cytochrome-P450 (CYP) isoenzymes

that are encoded in humans by 57 genes of 3 major families (Ingelman-Sundberg, 2004). Functional variants of the *CYP1A2*, *CYP2D6*, *CYP2C8/9*, *CYP2C19* and *CYP3A4/5* genes are of particular interest because they have been associated with altered clinical outcomes (Evans and Relling, 1999; Ingelman-Sundberg, 2004). Other known genetic variants affecting drug exposure include conjugation enzymes, such as uridine-5'-diphospho-glucuronosyltransferase (UGT) and N-acetyltransferase 2 (NAT2), and drug transporters, including solute carrier (SLC) and ATP-binding cassette (ABC) transporter families (Kerb, 2006).

The main targets for the wanted effects, as well as the main metabolism and excretion pathways of the sleep-wake therapeutics introduced in the previous paragraphs are summarized in **Table 1**. In the following section, known genetic differences in pharmacodynamics and pharmacokinetics of these drugs and drug classes will be reviewed. The contents of this section have been elaborated and updated based on a recent comprehensive overview (Holst et al., 2016). For that purpose, PubMed searches were performed between March 2015 and July 2018, including as search terms all generic drug names mentioned below AND ('pharmacogenetics' OR 'polymorphism' OR 'CYP' OR 'therapy'). A total of 79 references was identified, yet those articles whose content was unrelated to the present review are not cited here.

Pharmacotherapy of Insomnia Disorder and Parasomnias

Benzodiazepines, Z-drugs and barbiturates

Genetic variants of the α subunits of $GABA_A$ receptors alter the sensitivity to benzodiazepines and Z-drugs in transgenic animals (Tobler et al., 2001; Cope et al., 2004; Kopp et al., 2004), the treatment responses to antiepileptic drugs (Hung et al., 2013), and the sensitivity towards diazepam in alcoholic patients (Iwata et al., 1999). No studies on the relevance of $GABA_A$ receptor polymorphisms for variable hypnotic effects of benzodiazepines and Z-drugs in insomnia patients are currently available.

Most benzodiazepines and Z-drugs are degraded by CYP3A4/5 and CYP2C19 isoenzymes (Hohmann et al., 2016). Genetic variants of these enzymes affect the pharmacokinetics of various members of these drug classes (Park et al., 2006; Shen et al., 2013). Indeed, individual CYP isoenzyme metabolizer status is important for the correct dosing of these hypnotics, to optimize efficacy and avoid adverse actions, such as daytime impairment and next-morning sedation (Lozupone et al., 2017).

Some benzodiazepines (e.g., lorazepam, clonazepam, nitrazepam) are glucuronidated by UGT isoenzymes or acetylated by NAT2. Glucuronidation is a xenobiotic elimination reaction mainly occurring in the liver. Polymorphisms in some UGT genes affect lorazepam clearance. One case documented prolonged sedation after lorazepam, due to absence of the isoenzyme UGT2B7 (Siller et al., 2014). Furthermore, *NAT2* polymorphisms causing "slow acetylator" phenotypes impair the metabolism of clonazepam *in vitro* (Toth et al., 2016).

Dual orexin receptor antagonists

While genetic variants of HCRTR1/2 receptors and Hcrt synthesis are frequent (Thompson et al., 2014), their functional and pharmacological significance are not well understood. The current development of Hcrt receptor antagonists as novel hypnotics should take these genetic variants into account, to better understand the variability in drug efficacy and side effects (Hoyer and Jacobson, 2013; Thompson et al., 2014). For example, *in vitro* and *in vivo* characterization of the metabolism and disposition of suvorexant in humans determined that CYP3A4/5 are the predominant enzymes mediating oxidation of this compound (Cui et al., 2016).

Antihistamines

Large inter-individual differences are observed in the sedative effects of diphenhydramine, which appear to be due to drug metabolism rather than genetic variants of His receptors. The isoenzymes CYP2D6, CYP1A2, CYP2C9, and CYP2C19 contribute to diphenhydramine metabolism (Akutsu et al., 2007). Three CYP2D6 ultra-metabolizers reported paradoxical excitation rather than sedation on diphenhydramine treatment (de Leon and Nikoloff, 2008), and the *CYP2D6*10* allele was identified as a risk factor for antihistamine-induced sleepiness in Japanese adults (Saruwatari et al., 2006).

Sedating antidepressants and antipsychotics

Pharmacogenetic studies of mirtazapine established several polymorphisms that modulate its hypnotic and antidepressant efficacy. For example, the c.-998G>A polymorphism (SNP-Id: rs6311) of the gene encoding the 5-HT_{2A} receptor (*HTR2A*) determined mirtazapine-induced sleep improvements in patients with major depressive disorder (MDD) (Kang et al., 2007). Mirtazapine also binds to DA, NE and ACh receptors. Consistent with this pharmacological profile, also rs28363170 of the *DAT1* gene encoding the dopamine transporter (DAT; *aka* SLC6A3, solute carrier family 6 member 3), and distinct polymorphisms of *ARRB1* (β arrestin 1)*, COMT* (catechol-O-methyltransferase), *MAOA* and *MAOB* (monoamine oxidase isoenzymes A and B) genes affect responses to mirtazapine in patients with MDD (reviewed in (Holst et al., 2016)). These studies illustrate that sleep-promoting agents may act on multiple systems, and polymorphisms of genes regulating different neurotransmitters may mutually influence the efficacy of a given drug.

Polymorphisms of the *HTR2A* gene were also associated with treatment outcomes in depressed patients treated with SSRIs (Kato and Serretti, 2010). The variants c.371T>C of *HTR1B* (5-HT_{1B} receptor; SNP-Id: rs130060) and c.102C>T of *HTR2A* (SNP-Id: rs6313) affect binding affinity of the 5-HT_{2A} receptor antagonist, ketanserin (Brüss et al., 1999; Holmes et al., 2007). These

polymorphisms may modulate slow wave sleep promotion by 5-HT_{2A} receptor antagonists currently in development as novel hypnotics.

Apart from genetic differences in drug targets, genetically determined metabolizer status modifies clearance of doxepin (metabolized by CYP2D6, CYP2C9 and CYP2C19) (Kirchheiner et al., 2002) and (es)mirtazapine (primarily metabolized by CYP2D6) (Brockmöller et al., 2007). Fatal poisoning with both drugs was associated with defective CYP2D6 enzymes (Neukamm et al., 2013). Nevertheless, systematic review of the data indicates that more data are needed to conclude that CYP2D6 poor metabolizers are more prone to adverse effects of doxepin (Haufroid and Hantson, 2015). Driving performance in healthy volunteers was more impaired after esmirtazapine administration in poor rather than in rapid CYP2D6 metabolizers (Ramaekers et al., 2011).

Pharmacotherapy of Circadian Rhythm Sleep-Wake Disorders

Melatonin and melatonin analogues

Several polymorphisms in the melatonin receptor genes, *MTNR1A* and *MTNR1B*, were identified (Ekmekcioglu, 2006), and *MT2* receptor gene variants were associated with type-2 diabetes (Karamitri et al., 2013). One study suggested a relevant association between polymorphism rs2119882 of *MTNR1A* (proposed to affect promoter activity) and insomnia symptoms in schizophrenia (Park et al., 2011). The development of melatonin receptor agonists for insomnia and circadian rhythm sleep-wake disorders would benefit from pharmacogenetic studies, taking into account functional polymorphisms of melatonin receptors.

Melatonin is synthesized from 5-HT, metabolized in the liver almost exclusively by CYP1A2, and excreted as sulfphatoxymelatonin in urine (Claustrat et al., 2005). The plasma concentration of melatonin after oral ingestion was higher in individuals with *1A/*1A than with *1F/*1F genotypes of *CYP1A2* (Härtter et al., 2006). Furthermore, autistic patients with slow CYP1A2 metabolism due to *1F/*1A or *1A/*1A genotypes showed decreasing potency of melatonin to improve sleep problems

(Braam et al., 2013). Finally, Chinese carriers of a *1A and other *CYP1A2* variants appear to metabolize agomelatine more slowly than carriers of the *1F allele (Song et al., 2014). Interestingly, sulphatoxymelatonin was recently proposed as a potential biomarker of brain 5-HT status in severe genetic disorders affecting 5-HT biosynthesis (Batllori et al., 2017).

Pharmacotherapy of Central Disorders of Hypersomnolence

(Ar)Modafinil and stimulants

Individual effects of standard doses of (ar)modafinil and stimulants such as methylphenidate and amphetamines have been associated with genetic variants of proteins regulating endogenous neurotransmitter degradation and transmission. For example, the activity of the monoamine-metabolizing enzyme, COMT, depends on several known genetic variants, including the functional c.472G>A (p.Val158Met) polymorphism (SNP-Id: rs4680) (Chen et al., 2004). This common valine-to-methionine substitution drastically reduces enzymatic activity, leading to elevated prefrontal cortex (PFC) dopaminergic tone in Met/Met homozygotes when compared to Val/Val homozygotes (Tunbridge et al., 2006). The treatment response with modafinil in narcolepsy patients differs widely among COMT genotypes. To control EDS, patients (female and male) with the Val/Val genotype of rs4680 need almost 100 mg more modafinil per day than patients with the Met/Met genotype (Dauvilliers et al., 2002). Intriguingly, as will be outlined below, the impact of this polymorphism on modafinil's efficacy may be opposite in narcolepsy patients and sleep-deprived healthy volunteers.

Apart from genetic variance modulating monoaminergic neurotransmission, variants in the gene encoding the P-glycoprotein drug transporter ABCB1 (ATP Binding Cassette Subfamily B Member 1) may partly explain individual therapeutic response to modafinil treatment in narcolepsy (Moresco et al., 2016).

Both, the Val-allele of rs4680 of *COMT* and the 9R-allele of rs28363170 of *DAT1* (see below) were associated with a pronounced response to methylphenidate (Kereszturi et al., 2008; Froehlich

et al., 2011) and enhanced risk of methamphetamine-induced psychosis and abuse (Ujike et al., 2003; Li et al., 2004). Preliminary data further indicate that CYP2D6 extensive/ultra-rapid metabolizers could show an elevated risk for central nervous system risk adverse effects of methamphetamine (Haufroid and Hantson, 2015). Yet, more work is needed to confirm this association

Venlafaxine

Converging evidence from multiple studies indicates that CYP2D6 poor metabolizers are especially prone to adverse effects caused by venlafaxine (Haufroid and Hantson, 2015), whereas no significant association with clinical response was found with polymorphisms of the *ABCB1* gene (Moresco et al., 2016).

Caffeine

Wake promotion and sleep disruption by the adenosine receptor antagonist, caffeine, are highly variable in patients and healthy people. The reasons for the pronounced inter-individual differences in caffeine effects on sleep remain incompletely understood. Shared environmental factors contribute to poor sleep quality associated with sustained high caffeine consumption (Treur et al., 2018). In addition, a population-based survey in roughly 1000 participants indicated that caffeine reduces sleep efficiency more potently in G/A allele carriers than in G/G homozygotes of polymorphism rs73598374 of the gene encoding the adenosine metabolizing enzyme, adenosine deaminase (Mazzotti et al., 2011). This study, however, was not controlled and awaits replication.

Caffeine is mainly metabolized by CYP1A2, which shows 10- to 200-fold inter-individual differences in enzymatic activity (Fredholm et al., 1999; Gunes and Dahl, 2008). Consistent with the notion that the rate of caffeine metabolism is heritable (Rasmussen et al., 2002), a common C/A

polymorphism in intron 1 of the *CYP1A2* gene (SNP-Id: rs762551) was found to affect caffeine half-life in blood plasma, such that A/A-allele carriers (*CYP1A2*1F*) metabolize caffeine faster than C-allele carriers (Sachse et al., 1999). Nevertheless, health status, gender and age, as well as lifestyle factors (such as habitual smoking and caffeine consumption, both known to induce CYP1A2 enzymatic activity), also play important roles for the metabolism of caffeine to its primary metabolite, paraxanthine (e.g., Urry et al., 2016).

Disturbed sleep causes some people to voluntarily abstain from caffeine. Genome-wide association (GWA) studies examined genetic contributions to caffeine consumption in humans. In 47'341 participants of European descent, two polymorphisms regulating transcriptional activation of CYP1A2 determined habitual caffeine intake, one located in the bidirectional promoter region of the *CYP1A1-CYP1A2* locus (SNP-Id: rs2470893) and one located in the aryl hydrocarbon receptor (*AHR*) (SNP-Id: rs4410790) gene (Cornelis et al., 2011). Intriguingly, a second study with more than 10'000 participants of European ancestry, located two other polymorphisms in the same genes, rs2472297 (*CYP1A1-CYP1A2*) and rs6968865 (*AHR*) (Sulem et al., 2011). These GWA studies support a role for CYP1A2 in the pharmacogenetics of caffeine. In addition, variants of *ADORA2A* (gene encoding adenosine A_{2A} receptors) also influence caffeine preference (Cornelis et al., 2011) and sleep disruption by caffeine (Rétey et al., 2007; Byrne et al., 2012).

Because melatonin is also degraded by CYP1A2, caffeine and melatonin compete for the same metabolizing enzyme. The half-life of caffeine during melatonin release may be prolonged and, in turn, caffeine consumption may delay the nocturnal peak of melatonin (Härtter et al., 2006; Braam et al., 2013). Habitual caffeine intake should, thus, be taken into account to understand individual efficacy of melatonin and novel melatonin receptor agonists.

γ-Hydroxy-butyrate (GHB)

In patients suffering from narcolepsy, GHB is currently used as first-line treatment of EDS

and cataplexy. So far, no studies have investigated the relevance of functional genetic variants of $GABA_B$ receptors nor polymorphisms related to GHB metabolizing pathways for individual drug responses in narcolepsy patients. By contrast, GHB intolerance was proposed to possibly arise from reduced activity of the GABA metabolizing enzyme, succinic semialdehyde dehydrogenase (Berner, 2013).

Pharmacotherapy of Sleep-Related Movement Disorders

Dopamine $D_{2/3}$ receptor agonists

Polymorphisms of *DRD2* and *DRD3* genes (encoding dopamine D_2 and D_3 receptors) impact the effects of the dopamine receptor agonists used to treat RLS (Agundez et al., 2013). Pharmacogenetic evidence also linked a *Ser9Gly* polymorphism of *DRD3* (SNP-Id: rs6280) with response to pramipexole in Parkinson's disease (PD) patients, but not with the *Taq1A* polymorphism of *DRD2* (SNP-Id: rs1800497) (Liu et al., 2009). In another study, however, both rs1800497 and a *MspI* polymorphisms of *DRD3* (SNP-Id: rs4646996) were related to discontinued use of pramipexole and ropinirole in PD (Arbouw et al., 2009).

The D_2 receptor agonist ropinirole is degraded by CYP1A2 and to a lesser extent by CYP3A4 (Kaye and Nicholls, 2000), whereas the metabolic pathways for pramipexole are not yet clear (Agundez et al., 2013). A polymorphism of the gene encoding the solute carrier protein SLC22A1 (SNP-Id: rs622342) was linked to higher doses of pramipexole and reduced survival time after initiation of L-dopa therapy (Becker et al., 2011). These effects may be caused by reduced drug uptake from the small intestine.

Ligands of $\alpha_2\delta$ subunit of voltage-gated calcium channels

Mutations and deletions of the *CACNA2D1* gene coding for the $\alpha_2\delta$ subunit family, which has five isoforms targeted by gabapentin and pregabalin, were linked to several medical disorders and increased sensitivity to opioid treatment (Rhodin et al., 2013). Moreover, a *CACNA1A* mutation in mice leading to impaired G protein-coupled inhibition was associated with reduced sleep induction by adenosine and wake promotion by caffeine (Deboer et al., 2013). Interestingly, recent evidence indicates that genetic variants of *CACNA1C* are associated with sleep latency and sleep quality (Byrne et al., 2013; Parsons et al., 2013). It may, thus, be expected that such polymorphisms modulate the efficacy of drugs or environmental influences that affect sleep.

Gabapentin-like compounds undergo negligible metabolism and are primarily eliminated as unchanged drug by renal excretion. The c.1507C>T polymorphism (SNP-Id: rs1050152) of the gene encoding the solute carrier protein SLC22A4 affects gabapentin transport *in vitro*, yet homozygous T-allele carriers showed no enhanced renal clearance of gabapentin when compared to carriers of the 'wildtype' C-allele (Urban et al., 2007).

Pharmacogenetic Dissection of Sleep-Wake Circuitries in Humans

As mentioned above, converging lines of research employing optogenetic and chemogenetic methods in animal models have pointed to new structures and pathways regulating sleep and wakefulness. For example, dopaminergic signaling appeared for a long time to have no crucial role in sleep-wake regulation. Accumulating evidence now suggests that antagonistic adenosinergic-dopaminergic interactions particularly in the striatum play important roles in sleep-wake regulation (for reviews, see, Lazarus et al., 2017; Wisor, 2018). Based on this evidence, A_{2A}-D_2 receptor positive striatopallidal cells may serve as new target for therapeutic intervention in sleep-wake disorders. Preclinical human pharmacology provides a bridge between basic (sleep-wake) research and clinical (sleep-wake) medicine and is an essential step in the development of novel (sleep-wake) therapeutics.

Rational treatments of sleep-wake disorders should strengthen the physiological processes underlying sleep-wake regulation. According to this rationale, an 'ideal' novel hypnotic can be expected to promote the same physiological processes that underlie elevated sleep need and increased sleep intensity, as reflected by the prevalence of theta/alpha (~ 6-10 Hz) and delta (< 4 Hz) frequency activity in the electroencephalogram (EEG) in wakefulness and sleep. Sleep deprivation, the strongest challenge of the sleep-wake dependent, homeostatic facet of sleep-wake regulation, not only alters in highly predictable fashion electrical brain activity in these frequencies, but also impairs a wide range of measures derived from neurobehavioral performance tasks. In the laboratory, neurobehavioral deficits of sleep deprivation are accurately indexed by increased lapses and slowed reaction times on the psychomotor vigilance task (PVT). This task has been considered a gold-standard measurement of sustained vigilant attention in sleep-wake research (Lim and Dinges, 2010). Performance on the PVT is reliably impaired by elevated sleep need and reflect distinct changes in neuronal activity (Nir et al., 2017; Maire et al., 2018). Importantly, these consequences of sleep deprivation vary widely among individuals, and are in part genetically determined (Van Dongen et al., 2004; Lim et al., 2012). Intriguingly, however, the neurophysiological and neurobehavioral variables do not typically show a clear association with each other, but rather develop seemingly independently. Thus, it has been suggested that the neurophysiological and neurobehavioral consequences of sleep loss are likely governed by separate mechanisms. In the following section, an experimental pharmacogenetic approach to systematically dissect these sleep-wake regulatory processes in healthy humans will be outlined. Collectively, the results demonstrate distinctly different roles for adenosinergic and dopaminergic pathways in the regulation of sleep-wake dependent neurophysiological and behavioral functions of the brain.

ADOAR2A gene variants contribute to caffeine sensitivity and neurophysiological and behavioral effects of sleep deprivation

Through competitive blockade of adenosine A_1 and A_{2A} receptors in the central nervous system, caffeine attenuates the build-up of sleep pressure during wakefulness and delays the endogenous circadian clock (Landolt et al., 2004; Burke et al., 2015). The interference with these physiological sleep-wake regulatory mechanisms can disturb the quality of sleep (Clark and Landolt, 2017). The heritability of coffee attributed sleep disturbances equals roughly 40 % (Luciano et al., 2007). Caffeine is the major psychostimulant ingredient of coffee (Fredholm et al., 1999), whereas blockade of A_{2A} receptors is responsible for the wake-promoting action of caffeine (Huang et al., 2005). The human *ADORA2A* gene is located on chromosome 22q11.2, and functional genetic variation of *ADORA2A* is an important determinant of sleep disruption by caffeine. More specifically, a combined sleep deprivation and caffeine study provided evidence that the c.1976T>C polymorphism of *ADORA2A* (SNP-ID: rs5751876) modulates individual sensitivity to subjective and objective effects of caffeine on sleep (Rétey et al., 2007). Remarkably, this notion was confirmed in a large GWA study in 2'402 twins and their families (Byrne et al., 2012). The polymorphism rs5751876 forms linkage-disequilibria with several other variants of *ADORA2A* that modulate actions of caffeine on sleep and attentional domains that are commonly impaired by sleep deprivation (Bodenmann et al., 2012; Renda et al., 2015). In addition, caffeine sensitive and insensitive individuals appear to be differently affected by sleep loss (Rétey et al., 2006). This observation supports the notion that the functional state of A_{2A} receptors determines the accumulation of sleep need during prolonged wakefulness, both in mice and humans (Hayaishi et al., 2004; Bodenmann et al., 2012; Landolt et al., 2012; Rupp et al., 2013).

Adenosine A_{2A} receptors, dopamine transporters and dopamine D_2 receptors are co-localized in the striatum

The distribution of adenosine receptors in the central nervous system is highly heterogeneous. The A_{2A} receptor subtype is primarily expressed in the striate nuclei (caudate

nucleus, putamen, nucleus accumbens [NAc], globus pallidus) and olfactory tubercle (**Figure 2**). Accumulating evidence suggests that the striatum, the NAc in particular, plays critical roles in wake promotion by caffeine and in sleep-wake regulation (Lazarus et al., 2011; Zhang et al., 2013; Holst and Landolt, 2015). Apart from widespread glutamatergic inputs from several cortical and subcortical areas, the striatum receives dopaminergic inputs via axons originating in the *substantia nigra pars compacta* and the ventral tegmental area (VTA) of the brainstem. Extracellular dopamine levels in NAc and medial PFC fluctuate across sleep-wake states in rats (Lena et al., 2005). Combined behavioral, chemogenetic and optogenetic manipulations in freely moving mice suggest a fundamental role for the VTA dopaminergic circuitry in maintaining wakefulness and linking motivated behaviors with sleep-wake regulation (Eban-Rothschild et al., 2016; Oishi et al., 2017a).

Similar to adenosine A_{2A} receptors, also the dopamine re-uptake transporter (DAT) is highly expressed in the striatum (**Figure 2**). The DAT transports extracellular dopamine from the synaptic cleft into the pre-synaptic terminals for repackaging into vesicles. The deletion of the *dat* gene in mice reduces NREM sleep time and increases wakefulness (Wisor et al., 2001). Intriguingly, the *Dat*$^{-/-}$ knock-out mice are hypersensitive to the wake-promoting effects of caffeine. More specifically, relative to wildtype littermates, the knock-out animals exhibit a 3- and 5-fold greater increase in wake time after 2.5 and 10 mg/kg caffeine administration when compared to vehicle (Wisor et al., 2001). Based on these data in animals, it was hypothesized that functional variance not only in *CYP1A2* and *ADORA2A* (see above) but also in the *DAT1* gene may modulate the response to caffeine in humans.

DAT1 genotype modulates caffeine sensitivity and neurophysiological and behavioral effects of sleep deprivation

The human *DAT1* gene contains a common VNTR polymorphism in its 3'-untranslated region. Linkage and associations of this polymorphism (SNP-ID: rs28363170) with various psychiatric

disorders (e.g., attention-deficit-hyperactivity disorder, PD, alcoholism, schizophrenia) have been reported, suggesting that it is functionally relevant (Pinsonneault et al., 2011). In addition, i*n vitro* studies revealed an effect of this polymorphism on gene expression (Pinsonneault et al., 2011). The VNTR can exist in forms of 3 to 13 repeats, but two alleles are most common: 9 repeats (9R) or 10 repeats (10R) of a 40-bp sequence in exon 15. Several studies in humans quantified striatal DAT availability with SPECT (single photon emission computer tomography) and PET (positron emission tomography): these studies consistently reported lower striatal DAT binding in 10R homozygotes when compared to 9R allele carriers. On average, 10R homozygotes exhibit 10-15 % lower striatal DAT availability than 9R allele carriers (Costa et al., 2011; Faraone et al., 2014). Are 10R homozygotes, thus, more sensitive to caffeine than 9R carriers, analogous to *Dat*$^{-/-}$ mice?

This seems to be the case. In a survey among 485 individuals, a significantly larger proportion of 10R homozygotes (39 %) rated themselves as being sensitive to psychostimulant action of caffeine when compared to 9R allele carriers (Holst et al., 2014). In the case of 9R homozygotes, only 2 out of 23 individuals (9 %) were caffeine sensitive. The respective number was 33 % in 9R/10R heterozygotes. A subsequent controlled study in the laboratory confirmed that the *DAT1* VNTR predicts the effect of caffeine on EEG markers of sleep need. The stimulant attenuated the rebound in EEG slow waves following prolonged wakefulness in *DAT1* 10R homozygotes only (Holst et al., 2014). From the perspective of sleep-wake regulatory mechanisms, it is important to note that this polymorphism associated with the repercussions of sleep deprivation on sleep EEG markers of increased sleep drive (Holst et al., 2014). In addition, it modulated time-on-task effects and performance instability on the PVT, as well as on the effects of the DAT inhibitor, modafinil, on markers of sleep need (Lim et al., 2012; Holst et al., 2014; Satterfield et al., 2017). Taken together, convergent findings in animals and humans suggest that A_{2A} receptors and DAT are involved in the wake-promoting effects of caffeine and modafinil. They further indicate that adenosine-dopamine interactions in the striatum are important for sleep-wake regulation and the behavioral consequences of sleep deprivation.

DRD2 genotype modulates neurophysiological and neurobehavioral consequences of sleep deprivation

Increasing evidence demonstrates the presence of co-expressed A_{2A}-D_2 receptor complexes on distinct subpopulations of medium spiny neurons, the principle neuronal cell type of the dorsal and ventral striatum (Azdad et al., 2009; Ferre et al., 2010; Casado-Anguera et al., 2016). Indeed, brain imaging demonstrates that D_2 receptors are mainly expressed in the striatum (**Figure 2**). Striatal outputs are primarily composed of two types of projection neurons: indirect medium spiny neurons (iMSNs) that express D_2-type receptors and direct medium spiny neurons expressing D_1-type receptors (Ferre et al., 2010; Yager et al., 2015). Activation of iMSNs causes a net inhibition of the thalamus, which is part of the fronto-striatal circuit (Yager et al., 2015). Brain imaging of human subjects while performing a working memory task revealed that gene variants encoding DAT and D_2 receptor proteins interact to regulate fronto-striatal circuit activity (Bertolino et al., 2009). Moreover, striatal D_2 receptor availability after sleep deprivation is reduced when compared to baseline (Volkow et al., 2012) and regulates brain activation during performance of a visual attention task (Tomasi et al., 2016).

The *DRD2* gene includes a functional c.957C>T polymorphism (SNP-ID: rs6277) that affects levels and stability of mRNA such that C-allele carriers exhibit 15–20% enhanced striatal D_2 receptor availability when compared to T-allele carriers (Hirvonen et al., 2009). This polymorphism alone and in interaction with the presence of either 9R and 10R alleles of *DAT1* was found to modulate the evolution of waking EEG markers of accumulating sleep pressure, subjective sleepiness, as well as performance on the PVT across prolonged waking (Holst et al., 2017). More specifically, individuals homozygous for the C allele of *DRD2* and the 10R allele of *DAT1* were more severely affected with attentional lapses after 40 hours of wakefulness than other genotypic variants. A recent study confirmed that homozygous carriers of the C allele of the *DRD2* c.957C>T polymorphism are

impaired by sleep deprivation in vigilant attention (Whitney et al., 2017). Remarkably, however, the same individuals were resilient to the effects of prolonged waking on reversal learning, a measure of cognitive flexibility (Whitney et al., 2017). Consistent with the notion that the consequences of sleep deprivation are trait-like but *task-specific*, the data collectively suggest that striato-thalamo-cortical dopaminergic pathways contribute to the regulation of neurophysiological and neurobehavioral consequences of sleep loss in humans.

COMT genotype modulates neurobehavioral consequences of sleep deprivation without affecting neurophysiological markers of elevated sleep need

The *COMT* gene encodes the main enzyme degrading catecholamines in the PFC, COMT, which regulates dopaminergic neurotransmission by converting DA to 3-methoxytyramine (Matsumoto et al., 2003). The genotype of the Val158Met polymorphism of *COMT* (SNP-Id: rs4680) has a consistent impact on PFC functioning (Egan et al., 2001; Tunbridge et al., 2006; Bodenmann et al., 2009b). Nevertheless, some effects of this genetic variant only become apparent when the DA system is challenged, such as after sleep deprivation (Bodenmann et al., 2009a; Satterfield et al., 2018; Valomon et al., 2018). More specifically, Val/Val, Val/Met and Met/Met allele carriers perform similarly in baseline. Yet, after a night without sleep, Val/Met heterozygotes produced twice as many attentional lapses than Met/Met homozygotes (Valomon et al., 2018). Furthermore, the wake-promoting agent modafinil is virtually ineffective in mitigating impaired PVT performance after sleep loss in Met/Met homozygotes. By contrast, in homozygous Val/Val allele carriers, the same dose of modafinil maintains virtually optimal performance throughout 40 h of wakefulness (Bodenmann et al., 2009a).

To test the hypothesis that PFC dopaminergic signaling regulated by COMT causally contributes to neurobehavioral and neurophysiological markers of sleep loss, the interaction of *COMT* genotype, tolcapone and sleep deprivation on lapses of attention and neurophysiological

markers of sleep-wake regulation was investigated in a controlled laboratory study. Tolcapone is a brain penetrant inhibitor of COMT that leads to specific increases in PFC dopaminergic tone without affecting striatal dopaminergic transmission (Farrell et al., 2012). It was expected that tolcapone would mitigate the effects of sleep deprivation primarily in Val/Val homozygotes because it counteracts the overactive COMT and associated deficit in PFC dopaminergic function. Unexpectedly, tolcapone had no beneficial effect in any COMT genotype. By contrast, it increased attentional lapses even further, particularly in Val/Met and Met/Met allele carriers (Valomon et al., 2018). The data suggest an inverted U-shape relationship between PFC dopaminergic signaling and sustained attention after sleep loss. They further demonstrate that beyond and above COMT genotype, a pre-existing sleep debt strongly impacts on the effects of a pharmacological increase of dopaminergic neurotransmission on brain functions.

In contrast to these behavioral effects, genetically determined and pharmacologically induced differences in COMT activity do not affect established EEG markers of elevated sleep pressure in wakefulness and sleep challenged by acute total sleep deprivation (Bodenmann and Landolt, 2010; Valomon et al., 2018).

Experimental human pharmacogenetics: converging evidence for distinct adenosinergic/ dopaminergic pathways mediating neurophysiological and behavioral consequences of sleep loss

Among the four major dopaminergic pathways in the brain, three pathways originating in the midbrain are especially important for interpreting the findings discussed above. They consist of the *nigrostriatal pathway* projecting from the substantia nigra to the dorsal striatum (caudate nucleus and putamen), which is involved in motor control; the *mesolimbic pathway* originating in the VTA and innervating several structures of the limbic system (including the NAc), which is associated with reward cognition, reinforcement and motivational salience; and the *mesocortical pathway*, also originating in the VTA yet having widespread projections to the cerebral cortex, being essential for

normal cognitive functions of the dorso-lateral PFC, attentional control, motivation and emotional processes. The regulation of DA metabolism and uptake and, thus, dopaminergic neurotransmission depends on the different pathways, such that DAT and D_2 receptors regulate nigrostriatal/mesolimbic circuit activity, while COMT controls dopaminergic transmission in the mesocortical pathway.

Taken together, the systematic human pharmacogenetic dissection of adenosine-associated loci and dopamine-related loci demonstrates that the distinct signaling pathways differently modulate the response to sleep loss and wake-promoting agents on neurophysiological markers of sleep need and neurobehavioral deficits (**Figure 3**). The *ADORA2A* c.1976T>C polymorphism (Rétey et al., 2007; Rupp et al., 2013), an *ADORA2A* haplotype (Bodenmann et al., 2012), the *DAT1* VNTR polymorphism (Holst et al., 2014; Satterfield et al., 2017), and the *DRD2* c.957C>T polymorphism (Holst et al., 2017; Whitney et al., 2017) modulate both, EEG and distinct behavioral markers of elevated sleep need and the effects of caffeine and modafinil on these markers. The findings suggest that striatal iMSNs, which co-express high densities of adenosine A_{2A} and dopamine D_2 receptors mediate these consequences of sleep loss. It is tempting to speculate that the NAc is essential in these processes. Thus, elegant studies in animal models have demonstrated that caffeine and modafinil promote wakefulness by blocking A_{2A} receptors on GABAergic neurons of the NAc that co-express A_{2A} and D_2 receptors (Lazarus et al., 2011; Qiu et al., 2016; Oishi et al., 2017b). These neurons have major projections to the ventral pallidum and may induce sleep by inhibiting the ascending arousal pathways and the thalamus.

In contrast to *ADORA2A*, *DAT1* and *DRD2*, genetic variation of *COMT* did not impact on neurophysiological markers of sleep need (Bodenmann et al., 2009a; Valomon et al., 2018). Nevertheless, *COMT* genotype and pharmacologic interference with PFC dopaminergic tone with modafinil and tolcapone consistently affect the consequences of sleep loss on PVT lapses (Bodenmann et al., 2009a; Valomon et al., 2018). Given that tolcapone leaves striatal dopaminergic neurotransmission unaltered, this finding strongly indicates that the mesocortical pathway

contributes to the regulation of attentional lapses during prolonged wakefulness without affecting sleep-wake regulatory mechanisms.

Concluding Remarks

Prospects of Pharmacogenetics for Personalized Sleep-Wake Medicine and New Drug Discovery

Not only gene polymorphisms, but a host of environmental factors, including epigenetics, as well as co-morbidity and co-medications, cause variability in expression and function drug targets and pharmacokinetic processes in each individual. The genotyping of single genes is, thus, of limited use for guiding individual pharmacotherapy. Rather, the implementation of deep phenotyping strategies to test individual target and enzyme functions likely provides a more promising approach to achieve personalized dosing of sleep-wake drugs (e.g., (Hohmann et al., 2016; Urry et al., 2016)).

Powerful new tools to interrogate sleep-wake regulating circuits have revealed new molecular and cellular markers, as well as novel network mechanisms and pathways that regulate wakefulness and sleep. While the ascending arousal system was first described as a reticular network of neurons projecting widely to the cortex and the spinal cord (Moruzzi and Magoun, 1949), it has become clear in the last few years that wakefulness and sleep are governed by distinct populations and subtypes of neurons (Varin and Bonnavion, 2018). Although specific, these neuronal systems are often redundant and reinforce each other. Future research should clarify their causal associations with sleep homeostasis and the circadian clock, as well as sleep and circadian rhythm disturbances, in humans. For example, it should be clarified whether A_{2A}-D_2 receptor positive striatopallidal neurons regulate sleep homeostasis, or rather promote sleep in the absence of motivational stimuli (cf. (Oishi et al., 2017b)). Such studies may identify critical targets within newly identified sleep and circadian pathways for pharmacological interventions.

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Legends to the Figures

Figure 1. Schematic representation of sleep-wake disorders according to the International Classification of Sleep Disorders (ICSD) currently amenable to pharmacotherapy for improved sleep and wake state (thus excluding sleep-related breathing disorders)**.** Blue shading: drugs used to improve sleep in insomnia disorder, parasomnias, and circadian rhythm sleep-wake disorders. Red shading: drugs to improve wake state in central disorders of hypersomnolence. Green shading: drugs to reduce periodic limb movements in sleep (PLMS) in sleep-related movement disorders. Mel = melatonin; $MT_{1/2}$ = melatonin MT_1 and MT_2 receptors; 5-HT = serotonin; $5\text{-}HT_{2C}$ = serotonin-2C receptor; GABA = γ-amino-butyric acid; $GABA_A$ = $GABA_A$ receptor; $GABA_B$ = $GABA_B$ receptor; His = histamine; H_1 = histamine H_1 receptor; H_3 = histamine H_3 receptor; VGCC = voltage-gated calcium channel; DA = dopamine; DAT = dopamine transporter; $D_{2/3/4}$ = dopamine D_2, D_3 and D_4 receptors; Ado = adenosine; $A_{1/2A}$ = adenosine A_1 and A_{2A} receptors; NE = norepinephrine; Hcrt = hypocretin.

↑ amplification of neurotransmission; ↓ inhibition of neurotransmission

Figure 2. A_{2A} receptors, dopamine transporters (DAT), and D_2 receptors are co-localized on dorsal and ventral striatal neurons. The distribution volumes (color-coded) of selective radioligands that bind to these receptors and transporters on the level of the basal ganglia in humans were reconstructed with single photon emission computer tomography (^{123}I-MNI 420) and positron emission tomography (^{11}C-cocaine and ^{11}C-raclopride) imaging. The Figure has been composed of published data by (Seibyl et al., 2012) and (Volkow et al., 2012).

Figure 3. Pharmacogenetic dissection of adenosinergic-dopaminergic pathways with caffeine (A_{2A} receptor antagonist), modafinil (DAT inhibitor), and tolcapone (COMT inhibitor) reveal different contributions of dopaminergic pathways to sleep-wake regulation and behavioral consequences of sleep loss. The mesolimbic/nigrostriatal dopaminergic pathway (blue) regulates neurophysiological markers of sleep homeostasis in wakefulness and sleep and contributes to impaired sustained attention. Together with animal studies, findings support the notion that the nucleus accumbens,

which expresses high densities of dopamine D_2 and adenosine A_{2A} receptors, may be an essential player in these functions. The mesocortical dopaminergic pathway (red) does not affect neurophysiological markers of sleep deprivation. COMT = catechol-O-methyltransferase. DAT = dopamine transporter.

Table 1. Currently available pharmacological treatments of sleep-wake disorders.

Drug class	Approved compound	Sleep-wake indication(s)	Wanted sleep-wake effect(s)	Main mode of action for sleep-wake effect	Main metabolism/ excretion pathways
Benzodiazepines	Quazepam Estazolam Flurazepam Triazolam Temazepam Clonazepam	Insomnia Parasomnias	Improved sleep	Positive agonistic modulation of $GABA_A$ receptors	CYP3A4/5, CYP2C19, UGT isoenzymes, NAT2
Z-drugs	Zolpidem (Es)Zopiclone Zaleplon	Insomnia	Improved sleep	Positive agonistic modulation of $GABA_A$ receptors	CYP3A4, aldehyde oxidase
Barbiturates	Butabarbital Secobarbital	Insomnia (rarely used)	Improved sleep	$GABA_A$ receptor agonism	CYP1A2, CYP2C9/10, CYP3A4
	Sodium oxybate	Narcolepsy	Reduced cataplexy and improved wake state (EDS)	GHB/$GABA_B$ receptor agonism	GHB dehydrogenase → succinic acid → Krebs cycle → CO_2 exhalation
DORA	Suvorexant	Insomnia	Improved sleep	Hcrt-1/2 receptor antagonism	CYP3A4/5, CYP2C19
Antihistamines	Diphenhydramine Doxylamine	(Insomnia)	Improved sleep	H_1 receptor antagonism	CYP2D6, CYP1A2, CYP2C9
TCA	Doxepine	Insomnia	Improved sleep	H_1 receptor antagonism	CYP2D6, CYP2C19
TeCA	Mirtazapine	Insomnia	Improved sleep	H_1 receptor antagonism, 5-HT_{2A} antagonism	CYP2D6, CYP1A2, CYP3A4
Melatonin	Melatonin/Circadin®	Adult insomnia ≥ 55 y;	Improved sleep and wake	$MT_{1/2}$ receptor agonism	CYP1A2 → Sulpha-

Drug class	**Approved compound**	**Sleep-wake indication(s)**	**Wanted sleep-wake effect(s)**	**Main mode of action for sleep-wake effect**	**Main metabolism/ excretion pathways**
agonists	(prolonged release)	N24HSWD; DSPD; transient insomnia; SAD	state		methoxymelatonin (urine), CYP3A4
	Ramelteon	Sleep onset insomnia in older adults	Improved sleep	$MT_{1/2}$ receptor agonism	CYP1A2, CYP3A4
	Tasimelteon	N24HSWD; transient insomnia	Improved sleep and wake state	$MT_{1/2}$ receptor agonism	CYP1A2, CYP3A4
	Agomelatine	MDD	Antidepressant/anxiolytic, beneficial effect on sleep	5-HT_{2C} antagonism/ $MT_{1/2}$ receptor agonism	CYP1A2, CYP3A4
Psychostimulants	Methylphenidate	Narcolepsy	Improved wake state (EDS)	NET-DAT inhibition	CES1
	Methamphetamine			NE, DA, and 5-HT release NET-DAT inhibition	Urinary excretion as parent drug and/or D-amphetamine
	Caffeine	n/a		$A_{1/2A}$ receptor antagonism	CYP1A2
Wake promoting agents	(Ar)Modafinil	Narcolepsy, shiftwork sleep disorder, OSA	Improved wake state (EDS)	Unknown, DAT inhibition	Amide hydrolysis, CYP-mediated oxygenation
5-HT/NE re-uptake inhibitor	Venlafaxine	MDD, narcolepsy	Reduced cataplexy	SERT/NET inhibition	CYP2D6
H_3 inverse agonist	Pitolisant	Narcolepsy	Improved wake state (EDS) and reduced cataplexy	H_3 receptor inverse agonism	CYP3A4, CYP2D6
D_2 agonists	Pramipexole	PD, RLS	Reduction of PLMS	$D_{2/3/4}$ receptor agonism	Urinary excretion of unchanged drug (> 90 %)
	Ropinirole				CYP1A2
	Rotigotine				CYP2C19, UGT enzymes
	Gabapentine	RLS, insomnia	Reduction of PLMS, improved sleep	Unknown, binding to $\alpha_2\delta$ subunit of VGCC	Urinary excretion of unchanged drug

DORA = dual orexin receptor antagonists; TCA = tricyclic antidepressants; TeCA = tetracyclic antidepressants; 5-HT = 5-hydroxytryptamine, serotonin; NE = norepinephrine; H_3 = histamine H_3 receptor; Hcrt = hypocretin; D_2 = dopamine D_2 receptor; N24HSWD = non-24-hour sleep-wake disorder; DSPD = delayed sleep phase disorder; SAD = seasonal affective disorder; MDD = major depressive disorder; OSA = obstructive sleep apnea; PD = Parkinson's disease; RLS = restless legs syndrome; EDS = excessive daytime sleepiness; PLMS = periodic limb movements in sleep; GHB = γ-hydroxybutyrate; H_1 = histamine H_1 receptor; $MT_{1/2}$ receptors = melatonin MT_1 and MT_2 receptors; 5-HT_{2A} = serotonin-2A receptors; 5-HT_{2C} = serotonin-2C receptors; DAT = dopamine transporter; SERT = serotonin transporter; NET = norepinephrine transporter; $A_{1/2A}$ receptors = adenosine A_1 and A_{2A} receptors; VGCC = voltage-gated calcium channels; CYP = cytochrome-P450 isoenzymes; UGT = uridine-5'-diphospho-glucuronyltransferase; NAT2 = N-acetyltransferase 2; CES1 = carboxylesterase 1; COMT = catechol-O-methyltransferase; MAOB = monoaminoxidase type-B.

Figure 1

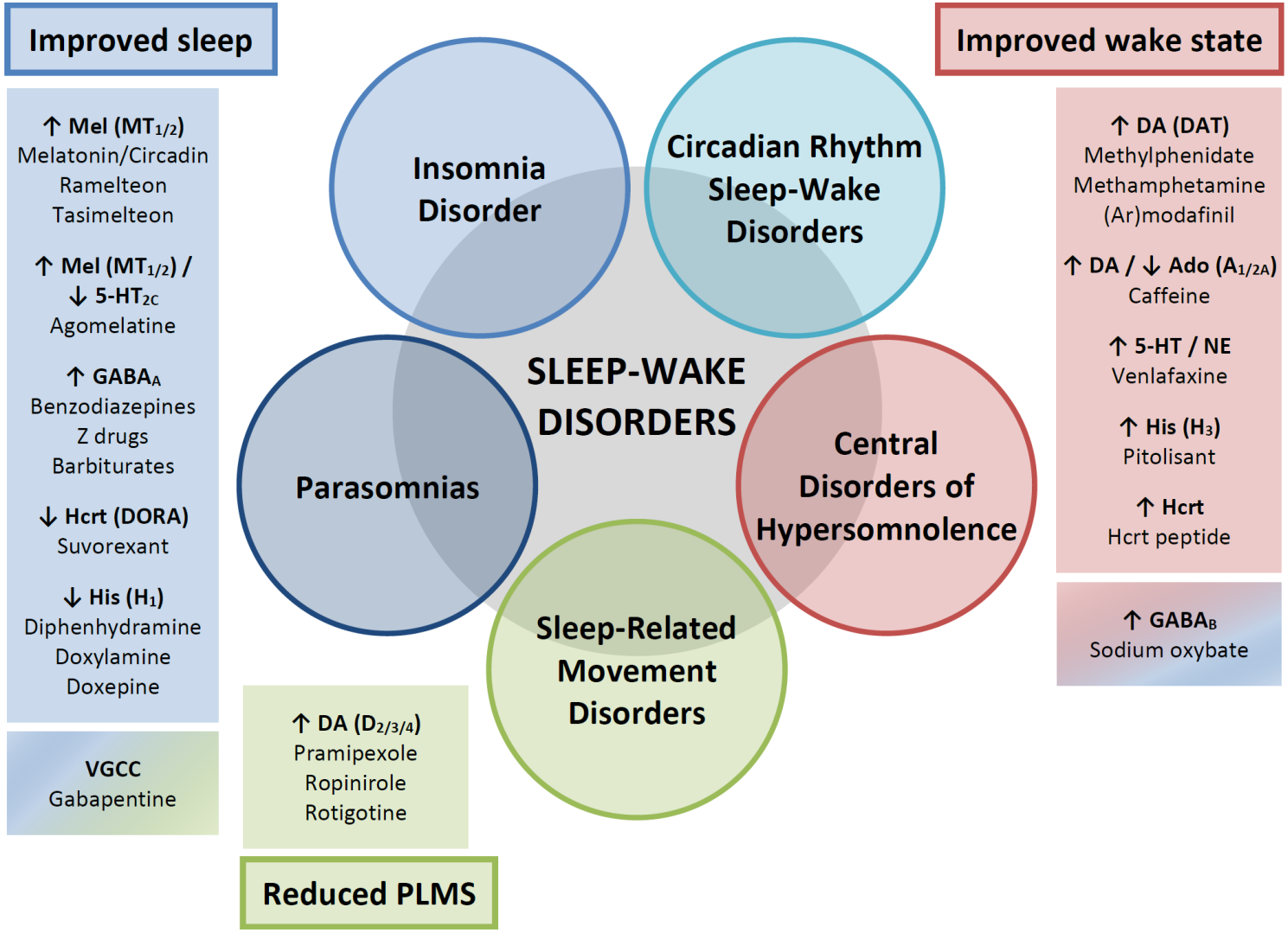

Improved sleep
↑ Mel ($MT_{1/2}$)
Melatonin/Circadin
Ramelteon
Tasimelteon
↑ Mel ($MT_{1/2}$) / ↓ 5-HT_{2C}
Agomelatine
↑ $GABA_A$
Benzodiazepines
Z drugs
Barbiturates
↓ Hcrt (DORA)
Suvorexant
↓ His (H_1)
Diphenhydramine
Doxylamine
Doxepine
VGCC
Gabapentine
Insomnia Disorder
Circadian Rhythm Sleep-Wake Disorders
SLEEP-WAKE DISORDERS
Parasomnias
Central Disorders of Hypersomnolence
Sleep-Related Movement Disorders
↑ DA ($D_{2/3/4}$)
Pramipexole
Ropinirole
Rotigotine
Reduced PLMS
Improved wake state
↑ DA (DAT)
Methylphenidate
Methamphetamine
(Ar)modafinil
↑ DA / ↓ Ado ($A_{1/2A}$)
Caffeine
↑ 5-HT / NE
Venlafaxine
↑ His (H_3)
Pitolisant
↑ Hcrt
Hcrt peptide
↑ $GABA_B$
Sodium oxybate

Figure 2

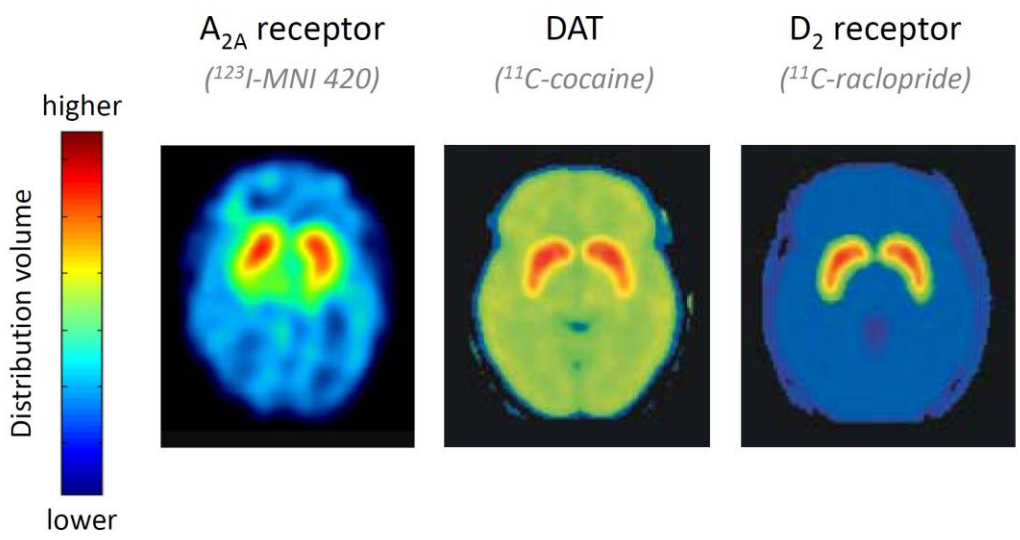
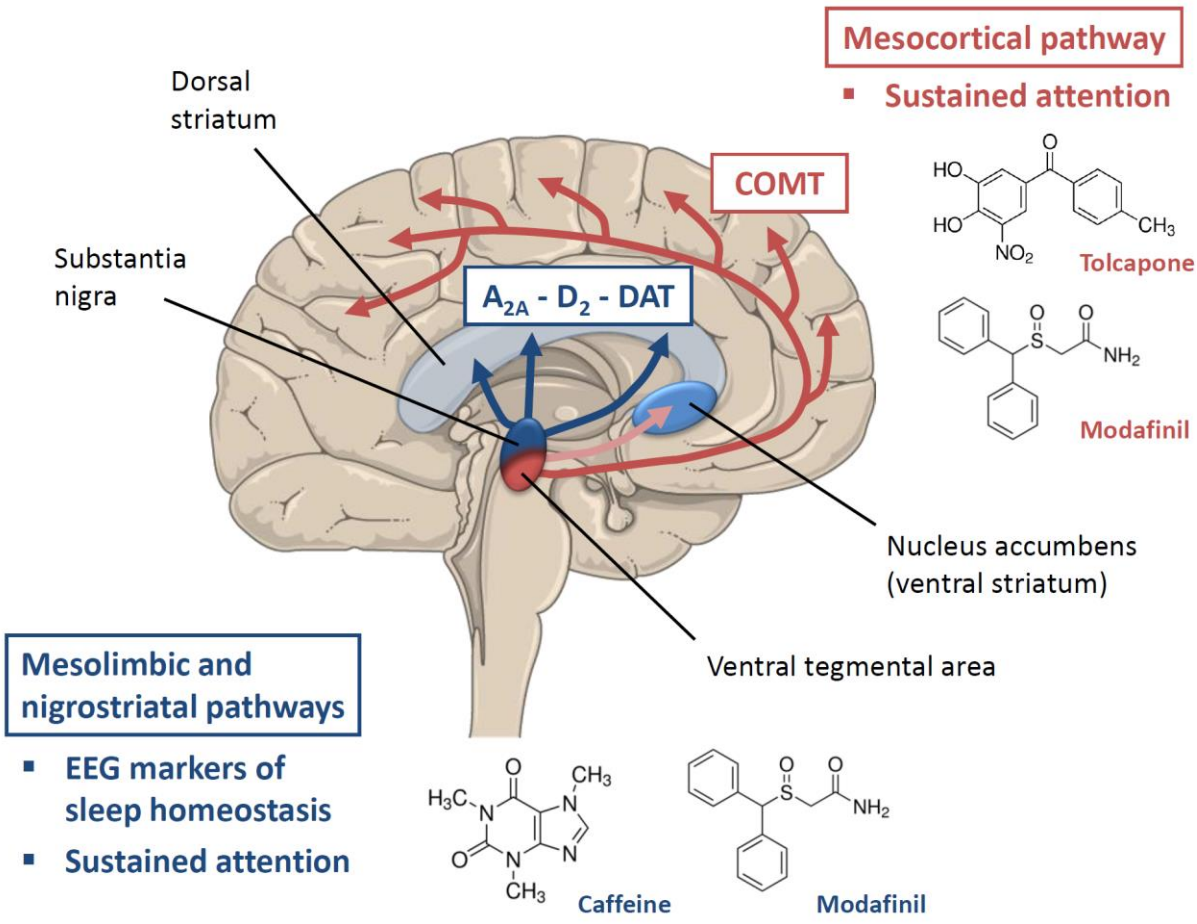

A2A receptor
(123I-MNI 420)
DAT
(11C-cocaine)
D2 receptor
(11C-raclopride)
higher
Distribution volume
lower

Figure 3


Mesocortical pathway
Sustained attention
Dorsal striatum
COMT
Substantia nigra
A_{2A} - D_2 - DAT
Tolcapone
Modafinil
Nucleus accumbens (ventral striatum)
Ventral tegmental area
Mesolimbic and nigrostriatal pathways
EEG markers of sleep homeostasis
Sustained attention
Caffeine
Modafinil